Flow Volume and Shunt Quantification in Pediatric Congenital Heart Disease by Real-Time Magnetic Resonance Velocity Mapping
A Validation Study

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Background—Flow quantification in real time by phase-contrast MRI (PC-MRI) may provide unique hemodynamic information in congenital heart disease, but available techniques have important limitations. We sought to validate a novel real-time magnetic resonance flow sequence in children.

Methods and Results—In 14 pediatric patients (mean age 5.2 ± 2.0 years) with cardiac left-to-right shunt, pulmonary (Qp) and aortic (Qs) flow rates were determined by nontriggered free-breathing real-time PC-MRI with single-shot echo-planar imaging combined with sensitivity encoding, which yielded 25 phase images per second at 2.7 × 2.7-mm in-plane resolution (field of view 30 × 34 cm²). Over a 9.5-second period that included 2 to 5 respiratory cycles, 16.6 ± 2.6 subsequent stroke volumes (range 13 to 22) were acquired in each vessel. Results were compared with conventional retrospectively ECG-gated PC-MRI. Mean Qp/Qs by conventional PC-MRI was 1.91 ± 0.64, and it was 1.94 ± 0.68 (mean ± SD) by real-time PC-MRI. For blood flow rate through pulmonary artery and aorta, we found differences of 2% to 3% (Bland-Altman analysis), with lower limits of agreement of −11% to −13% (mean − 2 SD) and upper limits of 18% to 19% (mean ± 2 SD), which demonstrated good agreement between both methods. Mean difference for Qp/Qs was 1%, with limits of agreement ranging between −18% and 22% (mean ± 2 SD). High repeatability but some flow overestimation was observed in vitro (pulsatile flow phantom) with real-time PC-MRI, whereas conventional PC-MRI was accurate. Beat-to-beat stroke-volume variation was 6.1 ± 2.3% in vivo and 3.7 ± 0.3% in vitro.

Conclusions—Beat-to-beat quantification of pulmonary and aortic flows and hence left-to-right shunt within a few seconds is reliable by nontriggered real-time PC-MRI with echo-planar imaging and sensitivity encoding. Good spatial/temporal resolution and a large field of view may render the sequence valuable for multiple applications in congenital heart disease. (Circulation. 2004;109:1987-1993.)

Key Words: magnetic resonance imaging • blood flow • heart defects, congenital • pediatrics • shunts

Blood flow quantification in thoracic vessels by conventional ECG-triggered phase-contrast cine MRI (PC-MRI) provides functional information in pediatric congenital heart disease. In the clinical setting, however, repeated measurements at multiple sites are often required, although they are time consuming. Other important limitations include variations of heart rate and respiration, as well as cardiac arrhythmia, each of which may severely degrade flow measurement results.

A nontriggered free-breathing PC-MRI technique with image acquisition in real time at frame rates of ≈ 25/s (ie, comparable to an echocardiographic frame rate) may overcome these limitations and provide more physiological information, such as the influence of respiration on flow volumes. Current MR techniques to obtain flow data in real time, however, are limited either in spatial or temporal resolution or use a small field of view (FOV), thus largely limiting slice angulation and/or examination of larger subjects because of backfolding.

We evaluated a novel real-time magnetic resonance (MR) phase-contrast pulse sequence using echo-planar imaging (EPI) in combination with sensitivity encoding (SENSE). This flow sequence provides both high spatial and high temporal resolution, as is appropriate for examination of great thoracic vessels in pediatric patients, but also allows for a large FOV, as is necessary for larger subjects. The purpose of...
the study was to validate the method in pediatric patients with cardiac left-to-right shunt. We chose this clinical setting because conventional PC-MRI, which was used as a reference for the real-time sequence in this investigation, has been evaluated recently in these patients for in vitro accuracy and in vivo reliability.9,10

### Methods

#### In Vivo Study Design

We enrolled into the study 14 consecutive patients (mean age 5.2±2.0 years, range 0.9 to 9.1; 11 females) with cardiac left-to-right shunt who had been referred clinically for MRI. Of these, 12 had sinus venous defect with partial anomalous pulmonary venous return and 2 secondum atrial septal defects. All patients were in sinus rhythm and had clinical/echocardiographic evidence of significant shunting. The study was approved by the institutional review committee, and informed written consent was obtained from parents or caretakers.

Each patient underwent MRI to measure through-plane flow in the ascending aorta and pulmonary artery. A standard PC-MRI measurement was repeated twice in each location. The mean value of both measurements served as reference and was compared with mean values of stroke volumes sampled by nontriggered free-breathing real-time single-shot echo-planar PC-MRI combined with SENSE (Table 1), over a data acquisition period of 9.5 seconds to include several subsequent and independently sampled stroke volumes, to determine overall stroke-volume variability with respiration in a free-breathing acquisition. Patients were sedated with midazolam and thiopental intravenously, and blood pressure, oxygen saturation, heart rate, and respiratory rate were monitored.

#### In Vitro Study Design

A polyvinyl chloride tube (luminal diameter 12.7 mm; wall thickness 2.4 mm) was embedded in a glass tube (diameter 100 mm, length 340 mm) filled with copper sulfate solution (3 mmol). The body coil was used for signal transmission, and a 5-element cardiac phased-array surface coil was used for signal detection. Plan scans in 3 orthogonal planes used ECG-triggered segmented-k-space turbo-field echo to allow double-oblique slice positioning for through-plane flow measurements in the pulmonary artery and ascending aorta. A free-breathing SENSE reference scan (<1 minute of scan time) was used to obtain sensitivity information necessary for application of the SENSE technique.10,12 Both standard and real-time PC-MRI acquisitions (Table 1) used a phase-correction algorithm provided by the manufacturer.

### MR Imaging Technique

All examinations were performed on a 1.5-T MR scanner (Philips, ACS-NT, R8, maximum gradient performance 30 mT/m, slew rate 150 T · m⁻¹ · s⁻¹). The body coil was used for signal transmission, and a 5-element cardiac phased-array surface coil was used for signal detection. Plan scans in 3 orthogonal planes used ECG-triggered segmented-k-space turbo-field echo to allow double-oblique slice positioning for through-plane flow measurements in the pulmonary artery and ascending aorta. A free-breathing SENSE reference scan (<1 minute of scan time) was used to obtain sensitivity information necessary for application of the SENSE technique.10,12 Both standard and real-time PC-MRI acquisitions (Table 1) used a phase-correction algorithm provided by the manufacturer.

### Real-Time and Standard PC-MRI Quantitative Flow Sequences

We designed a nontriggered, free-breathing, real-time PC-MRI sequence with blipped gradient-switching approach (EPI) combined with SENSE (Table 1). A matrix size of 112×128 and an FOV of 300×340 mm² resulted in a symmetrical in-plane resolution of 2.7×2.7 mm². To increase temporal resolution and shorten echo-train length, a SENSE-reduction factor of 4 combined with half-Fourier technique was applied, which reduced the number of actually acquired lines of k-space per repetition time (TR) to 19 (EPI factor). Interleaved velocity encoding was performed by application of a bipolar gradient after the slice-selection gradient (Figure 2). Thus, a complete phase-difference flow image was obtained every 39 ms, ie, ~25 flow images per second. An excitation angle of 40° was selected to provide sufficient contrast between moving and stationary spins.

As a reference, we used a standard T1-weighted cine phase-contrast gradient-echo sequence as described previously,10 using vector-ECG (VCG) for retrospective gating (Table 1). Both real-time and reference PC-MRI used a higher velocity-encoded value of 200 cm/s versus the in vitro value of 150 cm/s, to avoid phase wrap that

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**TABLE 1. Imaging Parameters for Conventional (Reference) and Real-Time PC-MRI With SENSE**

<table>
<thead>
<tr>
<th></th>
<th>Conventional PC-MRI</th>
<th>Real-Time PC-MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial resolution, mm</td>
<td>2.3×3.1×6</td>
<td>2.7×2.7×8</td>
</tr>
<tr>
<td>Repetition time, ms</td>
<td>15</td>
<td>19.4</td>
</tr>
<tr>
<td>Echo time, ms</td>
<td>6.5</td>
<td>4.9*</td>
</tr>
<tr>
<td>Flip angle, degrees</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>EPI factor</td>
<td>…</td>
<td>19</td>
</tr>
<tr>
<td>Echo-train length, ms</td>
<td>…</td>
<td>15.7</td>
</tr>
<tr>
<td>Half-scan factor</td>
<td>…</td>
<td>0.6</td>
</tr>
<tr>
<td>Temporal resolution, ms</td>
<td>~30</td>
<td>39</td>
</tr>
<tr>
<td>Signal averages</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>SENSE reduction factor</td>
<td>…</td>
<td>4</td>
</tr>
<tr>
<td>Scan time, s</td>
<td>60–180†</td>
<td>9.5</td>
</tr>
</tbody>
</table>

*Effective echo time.
†Depending on heart rate.
velocity, $V_{enc}$ is the velocity-encoding value, and $SD_v$ is the SD of magnitude images,\(^{13}\)

In the standard and real-time PC-MRI flow measurements of 1 subject (aged 4.5 years), we determined the signal-to-noise ratio (SNR) in phase images.\(^9\) To accelerate postprocessing for real-time PC-MRI, regions of interest were defined over 1 complete heart cycle (magnitude images) and copied to the remaining heart cycles, which left only a few frames for manual adaptation. Simultaneously recorded physiological data (VCG, respiration curves) were used for determination of stroke-volume variability during multiple truly repeated and nonaveraged stroke volumes are available from real-time flow data (Figures 1 and 3).

**Conventional Versus Real-Time PC-MRI**

The mean $Q_p/Q_s$ (pulmonary [$Q_p$] and aortic [$Q_s$] flow rate) ratios determined by conventional and real-time PC-MRI were 1.91±0.64 (range 1.17 to 3.33) and 1.94±0.68 (range 1.05 to 3.17), respectively. Bland-Altman analysis was applied to the log-transformed data because differences increased linearly with mean stroke volumes.\(^{15}\) Estimation of precision of the limits of agreement (defined as mean±2 SD) was based on calculation of 95% CIs. A mean value of 1.0 after antilog transformation is expected in the case of no difference between 2 tested methods.\(^{15}\)

When stroke volumes obtained with conventional and real-time PC-MRI were compared, a negligible difference of 3% was present in the pulmonary artery and 2% in the aorta, as reflected by a mean difference value of 1.03 and 1.02, respectively (Table 2). Upper and lower limits of agreement were 1.18 and 0.89 (pulmonary artery) and 1.19 and 0.87 (aorta). Thus, real-time flow measurements may differ from conventional PC-MRI by 18% above and 11% below for the pulmonary artery and by 19% above and 13% below for the aorta. For the flow ratio $Q_p/Q_s$, we found a mean difference of 1% (mean value 1.01), with upper and lower limits of agreement of 1.22 and 0.82, respectively.

**Repeatability and Stroke Volume Variation**

Excellent precision with a mean variation of only 2.3±1.9% was found in vivo between the 2 conventional flow measurements used as reference for the real-time MR technique. Real-time flow measurements were performed over 9.5 seconds to include more than 2 respiratory cycles. Depending on the heart rate, $16.6±2.6$ (mean±SD; range 13 to 22) truly repeated stroke volumes were available from each measurement (Figure 1). On average, stroke volumes varied from each other by $6.1±2.3$% (range 2.6% to 11.8%) in the 27 real-time data sets under sedated free-breathing conditions, with no significant difference between aorta and pulmonary artery.
Interobserver Variability

In 7 randomly selected patients, all stroke volumes in the ascending aorta and pulmonary artery (14 real-time and 28 conventional scans) were evaluated independently and in a blinded manner by 2 experienced observers (H.K. and Kerstin Berkemeier, RN). The mean difference for the averaged pulmonary stroke volume acquired with real-time PC-MRI was $-5\%$ (mean 0.95), with upper and lower limits of agreement of 1.09 (95% CI 1.00 to 1.19) and 0.83 (95% CI 0.76 to 0.91). For the averaged aortic stroke volume, the difference was $-4\%$ (mean 0.96), with upper and lower limits of agreement of 1.06 (95% CI 0.99 to 1.13) and 0.87 (95% CI 0.82 to 0.93). Negligible interobserver differences were found for conventional PC-MRI in the pulmonary artery, with a mean difference of $1\%$ and upper and lower limits of agreement of 1.07 (95% CI 1.03 to 1.11) and 0.96 (95% CI 0.93 to 0.99), as well as in the aorta, with a mean difference of $-1\%$ and upper and lower limits of agreement of 1.05 (95% CI 1.01 to 1.08) and 0.94 (95% CI 0.91 to 0.98), respectively.

SNR and VNR

SNR and VNR values are expressed as percentages of corresponding values of standard PC-MRI (which equals 100%). With real-time PC-MRI, SNR in the magnitude images was reduced to 13% (6%) in the aorta (pulmonary artery), whereas VNR in the phase images was only reduced to 93% (55%) of standard PC-MRI (Figure 4).

In Vitro Flow Measurements

Repeatability (ie, precision) of the manually obtained (“true”) flow values determined by stopwatch and graduated cylinder was excellent (error <1%), as was repeatability of the conventional PC-MRI measurements (error <2.2%). Pulsatile flow-phantom measurements with conventional and real-time PC-MRI correlated well with true flow, as reflected by the correlation coefficients of 0.999 for both techniques. The y-intercepts were negligible. Although the slope of 1.01 for conventional PC-MRI reflects close identity with “true” flow values ($y = 0.01 + 1.01x$; relative differences $-0.4\%$ to 4.7%; $P=NS$), a moderate overestimation (systematic error) was observed for real-time PC-MRI ($y = -0.03 + 1.26x$; relative differences 12.8% to 28.1%; $P<0.006$). During the 9.5-second data sampling period, 12 to 13 flow curves were registered. On average, stroke volumes differed by $3.7\pm0.3\%$.

Discussion

Why MR Flow Quantification in Real Time?

Over the past decade, conventional ECG-gated PC-MRI has been firmly established as a valuable technique to assess...
Real-Time MR Flow in Congenital Heart Disease

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Current Obstacles in Use of Real-Time MR Flow

A more widespread use of real-time MR flow in clinical routine, however, is hampered by important technical limitations of currently available techniques. Hjortdal et al used a real-time phase-contrast segmented k-space fast-field-echo MR technique with echo-planar readout. Although they were able to achieve adequate temporal and spatial resolution (phase-difference images every ~50 ms, pixel size 3.4×2.1 mm), this was only possible with a very small FOV of 9.0×13.6 cm. Therefore, owing to limitations from backfolding, the sequence is not suited for double angulation of slice position as is usually mandatory in the MR evaluation of congenital heart disease or for examination of larger subjects. Moreover, validation data for their MR flow method are lacking. Klein et al used a comparable MR sequence with a larger FOV in their adult population, but at the expense of considerably reduced temporal resolution (phase images every 124 ms, ie, 8 images/s). Eichenberger et al used real-time phase-contrast single-shot EPI. They achieved good temporal resolution (phase intervals of 37 ms, ie, 27 images/s) at the expense of limited spatial resolution (5.0×5.0 mm in-plane), which is likely to introduce systematic error from partial volume effects in pediatric patients.

Real-Time MR Flow With EPI and SENSE

Clinical Considerations

In this context, we present the first real-time MR flow quantification technique that combines both improved spatial (in-plane resolution 2.7×2.7 mm) and temporal (phase interval 39 ms) resolution, which is considered adequate for flow measurements in the great thoracic vessels in pediatric patients. The sequence also allows for a relatively large FOV and thus for more flexible applications in both pediatric and adult congenital heart disease. This is achieved by the use of single-shot EPI and a high SENSE-reduction factor of 4.

We validated this real-time MR flow sequence in comparison with standard retrospectively ECG-gated PC-MRI and demonstrated the reliability in the quantification of pulmonary and aortic flow rates and hence left-to-right shunt in pediatric congenital heart disease. Although a stroke volume can be assessed in a single heart beat by application of this real-time technique, scan time was extended to ~9.5 seconds to include more than 2 respiratory cycles and thus allow comparison of the mean stroke volumes with standard (reference) PC-MRI, by which an averaged stroke volume is acquired over multiple heart beats (Figure 3). There was almost no difference, and there was limited scatter of measurement results for aortic and pulmonary flow and for the ratio Qp/Qs compared with a standard PC-MRI protocol with a comparable spatial resolution.

Another result of the present study is the small variation (6.1±2.3%) of stroke volumes with respiration in both great arteries in sedated pediatric patients. In light of this, scan time may be shortened to only 1 to 2 seconds (instead of 9.5 seconds) to sample 1 to 3 stroke volumes. In contrast, a 10% decrease of aortic flow during inspiration was described in healthy adults. This demonstrates that the impact of respiration on flow in thoracic vessels must be considered when novel techniques for flow quantification are evaluated. For example, it is unknown at present whether and to what extent flow rate in the great thoracic vessels is attenuated by breath-holding. This question can now be addressed with real-time MR flow. Another advantage of real-time over conventional gated MR flow is that cardiac arrhythmia should no longer preclude safe and reliable flow measurements. It is now possible to analyze such flow data during postprocessing, because VCG curves displaying the arrhythmia and flow curves can be aligned. This enables the selection of usable...
flow curves for diagnostics in that, for example, a ventricular ectopic beat can be identified and such flow values rejected. In contrast, such flow data are usually nondiagnostic when conventional ECG-gated PC-MRI is used because of errors in phase reordering. This is important given that cardiac arrhythmia is frequently encountered in adult patients with congenital heart disease, who benefit most from noninvasive follow-up by MRI because Doppler echocardiography is often hampered by limited acoustic windows. Real-time MR flow provides a novel method to assess hemodynamics in this subgroup of patients.

The available degree of freedom in slice angulation and the good spatial/temporal resolution may extend the clinical and research applications of real-time MR quantitative flow in both pediatric and adult cardiovascular disease. It may be possible, for instance, to quantitatively determine immediate changes in the pulmonary flow rate in response to pharmaco-

cologically induced vasodilation in patients with pulmonary hypertension resulting from increased pulmonary arteriolar resistance. This may be especially useful in an interventional MR setting, allowing simultaneous pressure recording and flow assessment to determine rapid changes in pulmonary vascular resistance. 18

**Technical Considerations**

In the SENSE approach, an array of multiple, simultaneously operated receiver coils for signal acquisition (eg, cardiac 5-element phased-array surface coil) is used to spatially encode the MR signal as a function of the sensitivity of each coil element. 12 This allows the number of phase-encoding steps to be reduced by increasing the distance of readout lines in k-space (ie, parallel imaging) and thus accelerates acquisition, but at the expense of a lower SNR. 12 Compared with standard PC-MRI, a significant loss of SNR in real-time PC-MRI magnitude and phase images is present (Figure 4). This not only relates to the SNR penalty bounded by square root to the number of samples acquired but also contains noise from sensitivity maps as propagated in the SENSE reconstruction process, especially at higher SENSE reduction factors, such as those used in the present real-time sequence. 12 However, Conturo and Smith 19 demonstrated that phase images have an inherently better dynamic range than magnitude images that result in a signal-to-noise advantage in clinical flow imaging. They proposed that useful phase-angle information can be extracted even when magnitude images are very noisy, such as with rapid data collection techniques. 19 This may explain why VNR apparently was not a major limitation with real-time PC-MRI. Moreover, surprisingly, no obvious degrading effects of residual eddy currents (high-gradient switching rate with EPI) and concomitant fields (high-gradient amplitude) were obvious in the in vivo measurement results of the present study.

The main advantage of combining single-shot EPI with SENSE is to drastically reduce echo-train length while preserving high imaging speed. 8 To achieve this goal, we used a high SENSE reduction factor of 4. This may be beneficial for 3 reasons. First, a higher SNR is achievable when SENSE is used because EPI data are collected during the early part of T 1 * decay (which contains more signal). In contrast, when single-shot EPI is used without SENSE (ie, long echo-trains) data collection occurs in part beyond T 1 * decay (which contains little signal). Therefore, some of the signal-to-noise penalty from the use of higher SENSE reduction factors is compensated. Second, phase errors/spatial distortions that result from off-resonance effects such as magnetic susceptibility and chemical shift 20 or that are caused by local B 0 field inhomogeneities 21,22 are reduced with a shorter echo-train. Third, with a shorter echo-train, considerably shorter effective echo times are possible, thus diminishing the influence of turbulent flow. This may improve flow accuracy and image quality.

To avoid severe deterioration of image quality from back-

folding artifacts (due to the SENSE reconstruction process), no further foldover should occur during planning of the desired FOV. Therefore, we chose a relatively large FOV of 30×34 cm 2 to enable the use of a standardized real-time PC-MRI protocol at different body sizes and slice angulations with respect to geometric properties and gradient performance. As a result, however, the impact of SENSE recon-

struction may have been variable, depending on angulation and body size as related to the FOV.

Although smaller flip angles are generally thought to reduce systematic error in quantitative flow assessment from partial volume effects by decreasing the signal magnitude difference between flowing blood and surrounding tissue, 23 a more inflow-dependent acquisition with a flip angle of α=40° was considered important to enable clear vessel border detection in the corresponding magnitude images, thus avoiding major bias from displacement of regions of interest.

**In Vitro Performance**

Although we found high precision (repeatability) in vitro for real-time PC-MRI, some flow volume overestimation was present in the flow-phantom experiments, most likely because of partial volume effects, chemical shift, and susceptibility artifacts (eg, tube wall). 16 for which single-shot EPI is known to be sensitive. 20 The use of large (3-cm diameter) or very thin-walled (0.1 mm) 23 tubes and nonpulsatile low-flow conditions 8 has been shown to improve in vitro accuracy but does not resemble the pediatric measurement environment. Therefore, assessment of the accuracy of this real-time PC-MRI technique remains difficult, because both in vitro and in vivo, there is a lack of a true “gold standard.”

**Study Limitations**

No conclusions from the present data are applicable to children with valvular stenosis and turbulent blood flow. The borderline in-plane resolution of both real-time and reference PC-MRI may render flow volume measurements in smaller vessels at risk for flow underestimation due to partial volume effects. Only relative changes should be emphasized in SNR/VNR measurements, because absolute values may be influenced by interpatient variations and background filtering in the reconstructed images, which reduce the noise component. Although real-time magnitude and phase-image quality were acceptable, skilled observers and computer-assisted vessel border detection software were needed. However, some region-of-interest displacement may have occurred in
heart phases with slow flow, thus contributing to the small but statistically significant interobserver bias. In the in vitro experiments, the FOV was too large to ensure that 4-fold undersampling would lead to actual foldover in the single coil data, and therefore conclusions regarding the impact of SENSE acquisition and reconstruction on phase encoding of flow volume should be drawn with caution. An adopted FOV with a reduced matrix for a similar voxel size, however, would have been different from the real-time PC-MRI protocol used in vivo.

Conclusions

Stroke-volume quantification in great arteries and hence Q/Q estimation in a few heartbeats is reliable in children with cardiac left-to-right shunt by use of real-time PC-MRI with single-shot EPI and SENSE. Stroke-volume variation was small under free-breathing conditions. This real-time MR flow sequence combines high spatial/temporal resolution and a large FOV and may thus be valuable for multiple clinical and research applications in congenital heart disease.

Acknowledgments

We thank Johan van den Brink, PhD (Philips Medical Systems, Best, The Netherlands), for his contribution in programming the basic pulse sequence and Kerstin Berkemeier, RN, for her assistance in postprocessing of quantitative flow data. Research software was provided by Philips Medical Systems, Best, The Netherlands.

References

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Circulation. 2004;109:1987-1993; originally published online April 5, 2004; doi: 10.1161/01.CIR.0000126494.66859.A2
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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